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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/444,711	11/24/1999	TIMOTHY J. YEATMAN	114205.400	9003

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EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/25/2003

24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/444,711	YEATMAN ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,40,42,44,45,47 and 49-69* is/are rejected.

7)☒ Claim(s) *41, 43, 46 and 48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 39-69 are pending.

Claims 29-38 have been cancelled.

Claims 39-69 have been added.

Claims 39-69 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

3. The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on November 13, 2002 have been approved by the draftsman.

Withdrawn Objections

Specification

4. The disclosure is no longer objected to because the "Brief Description of the Drawings" section contains a figure legend/caption for figure 4e.

Claim Objections

5. Claim 29 is no longer objected to because it has been cancelled.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

6. The rejection of claims 29-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the cancellation of the claims.

Claim Rejections - 35 USC § 102

7. The rejection of claims 29-36 and 38 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 5,336,615 (August 9, 1994) is withdrawn in light of the cancellation of the claims.

8. The rejection of claims 29-36 and 38 under 35 U.S.C. 102(b) as being anticipated by Accession number AAQ46688 and Accession number AAR39706 of WO 93/14193 A (July 22, 1993) is withdrawn in light of the cancellation of the claims.

Claim Rejections - 35 USC § 103

9. The rejection of claims 29-38 under 35 U.S.C. 103(a) as being unpatentable by U.S. Patent number 5,336,615 (August 9, 1994) and Accession numbers AAQ46688 and AAR39706 of WO 93/14193 A (July 22, 1993) is withdrawn in light of the cancellation of the claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 39, 40, 42, 44, 45, 47, 49-52, 54, 56-58, 61, 62, 66 and 67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 39, 40, 42, 44, 45, 47, 49-52, 54, 56-58, 61, 62, 66 and 67 broadly claim an isolated polynucleotide encoding a mutant c-Src polypeptide, wherein

(a) said polynucleotide encodes a stop codon at nucleotides 1591 to 1593;

(b) the polynucleotide has a C to T transition mutation at nucleotide 1591, which encodes a polypeptide comprising an amino acid sequence consisting of SEQ ID NO:2;

(c) the recombinant construct that comprises the said polynucleotide, which is contained in a transgenic cell and the method for producing a mutant c-Src protein;

(d) an oligonucleotide that is capable of recognizing and distinguishing a mutant c-Src gene; and

(e) a diagnostic kit comprising the said oligonucleotide. The written description in this instant case only sets forth polynucleotide, SEQ ID NO:3, which encodes the mutant c-Src polypeptide comprising SEQ ID NO: 4. And the written description in this

case additionally only sets forth the oligonucleotide identified as SEQ ID NO: 5, a 3' mutant allele specific primer capable of recognizing the mutant c-Src gene, therefore the written description is not commensurate in scope with the claims drawn to any polynucleotide or oligonucleotide which may encode a mutant c-Src polypeptide or capable of identifying a mutant c-Src gene contained within vectors, host cells and diagnostic kits.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO: 3-5, the skilled artisan cannot envision the broadly claimed polynucleotides and oligonucleotides, as well as the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polynucleotides and corresponding polypeptides themselves are required. See *Fiers v.*

Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

There is no support for any polynucleotides other than SEQ ID NO: 3 that is capable of encoding a mutant c-Src polypeptide (SEQ ID NO: 4), wherein the said nucleic acid encodes a stop codon at nucleotides 1591 to 1593 and the polynucleotide is comprised within a vector and host cell. Nor is there support for any other oligonucleotide other than SEQ ID NO: 5 that is capable of recognizing and distinguishing a mutant c-Src gene and a diagnostic kit comprising the said oligonucleotide. Support for one polynucleotide, SEQ ID NO: 3 encoding the mutant c-Src polypeptide identified as SEQ ID NO: 4 is provided in the specification on pages 7-9 and support for the oligonucleotide identified as SEQ ID NO: 5 is found on page 11. However, no disclosure is presented regarding any other polynucleotide and

oligonucleotide sequences with the assigned capabilities are made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore the disclosure only evidences a nucleic acid, SEQ ID NO: 3 encoding a mutant c-Src polypeptide consisting of the specified 530 amino acids identified as SEQ ID NO: 4. The disclosure also only evidences an oligonucleotide, SEQ ID NO: 5 which is capable of recognizing and distinguishing a mutant c-Src gene set forth as SEQ ID NO: 3. The full breadth of the claims do not meet the written description provision of 35 U.S.C. 112, first paragraph.

11. Claims 51-56 and 66-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants broadly claim a transgenic cell containing a mutant c-Src polypeptide comprising SEQ ID NO: 4 within an expression vector and a method for producing the said polypeptide by culturing the transgenic cell. These claims read on a cell within a transgenic animal given that the term "isolated" is not denoted in describing the transgenic cell. The breadth of the claim reads on the implementation of the transgenic cell in both *in vitro* and *in vivo* assays.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Molec. Biol. 7, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same

construct (Cameron, 1997, Molec. Biol. 7, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins (1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of

nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species. Applicants can obviate the instant rejection by amending the claims to recite the term "isolated" before the recitation, "transgenic cell".

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 57-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 57 is vague and indefinite in the recitation "recognizing and distinguishing a mutant c-Src gene". It is not clear from the claim what the mutant gene is to be distinguished from or is it to be recognized and distinguished from the wild-type. Accordingly, the metes and the bounds cannot be determined.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 57-65 are rejected under 35 U.S.C. 102(b) as being anticipated by the 1997/1998 Stratagene catalog (page 118, 1997/1998). For 102 art rejection purposes the claims are read to the extent that optional agents are not required. The 1997/1998 Stratagene catalog discloses the Prime-It® II Random Primer Labeling Kit containing an instruction manual and hexanucleotides containing all possible 6-nucleotide sequences and inherently would be capable of recognizing and distinguishing a mutant c-Src gene comprising nucleotides 1 to 1593 of SEQ ID NO: 3 which encodes mutant polypeptide SEQ ID NO: 4.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 57-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over 1997/1998 Stratagene catalog (page 118, 1997/1998). The teachings of the 102(b) reference have been presented in the 102 art rejection above. For 103 art rejection purposes the claims are read to the extent that optional agents are required. This

reference does not teach a diagnostic kit optionally containing a positive control comprising a mutant c-Src gene and a negative comprising a wild-type c-Src gene.

Although the claims recite an optional clause, no positive recitation of the optional agents distinguishes the claim over the reference. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to include products exemplifying a positive and negative control. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art to place the negative and positive controls in a kit because it is a well-known convention in the art to place the recited elements in a kit for the advantages of testing efficacy, and convenience, as well as the recited elements would provide an efficient mode of diagnosis.

Allowable Subject Matter

18. Claims 41, 43, 46 and 48 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
March 20, 2003